REMARKS

Claims 28-33, and 54-88 and 93-104 constitute the pending claims in the present application. Applicants have amended claims 28, 54, 55, 80, 85 and 87. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Claim rejections under 35 U.S.C. 112

Claims 28-33, and 54-88 and 93-104 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement.

This section of the Office Action raises the following five issues:

(i) The Examiner alleges that Applicants have shifted the meaning of the term "increased biological activity" from one office action response to another and each shift results in a different rejection. The Office Action quotes the following section from the amendment filed on July 2, 2002 in support of its argument:

> *Applicants submit that the Office Action seem to have misinterpreted the claimed invention, which is partly directed to the discovery that serum albumin can serve as a "protein carrier" to a heterologous polypeptide inserted herein, and confers the inserted heterologous polypeptide an increased lifetime (half-life), and thus increased observed biological activity relative to the uninserted heterologous polypeptide (for example, see paragraph bridging pages 5 and 6).*

(ii) The Examiner alleges that the prosecution history shows that applicants argued that the full scope of the claims was enabled because (i) the role of SA is a carrier and (ii) the Office's rejection based on unpredictability in protein chemistry art does not apply to the instant invention.

(iii) The Examiner alleges that applicants argue that increased biological activity means 1000-fold more activity of EC binding peptide as disclosed in the specification, and the Office Action believes this to be the exception rather than the rule, as not every peptide is expected to

show such an increase in biological activity.

(iv) The Examiner maintains the enablement rejection for reasons of record provided in the three previous Office Actions because "specification does not teach how to make such construct that would increase 1000-fold more activity."

(v) The Examiner further argues that if Applicants maintain that the claimed invention is a product with 1000-fold more activity than the inserted peptide, then the written description rejection withdrawn in the Office Action mailed on 9-24-2003 will be reinstated (applicants believe the Examiner is referring to the Office Action mailed on 9-24-2002 as none was mailed on the stated date). Examiner further requests that applicants state what the true invention in the instant application before proceeding further.

Applicant's traverse this ground of rejection. Applicants respectfully contend that the Office Action has not fully considered the arguments presented by the Applicants in the previous Office Action Response. Applicants will address each of the above five points raised by the Office Action in order.

(i) With respect to the first issue, Applicants contend that the Office Action reflects a misconception as to the relationship between a carrier protein and biological activity. This is particularly evident in the previous office action, which alleges on page 3, lines 3-6, that "the Office will assume that increased half-life is increased biological activity in view of applicant's argument that albumin is a carrier protein, which suggests has the same meaning *i.e.* increased plasma stability."

The Office Action incorrectly asserts that if a peptide has an increased half-life when inserted into a carrier protein, then the chimeric albumin protein has an increased biological activity relative to the peptide. According to the Office, stability is a biological activity, and thus any type of chimeric protein which is more stable than the inserted peptide has a higher biological activity. Applicants disagree with this interpretation. Stability per se is not a biological activity. Applicants have asserted this point in the previous Office Action Responses and again reiterate this position. Furthermore, Applicants have defined the term "biologically

active" in the specification on pages 11, 2nd full paragraph as follows:

> "biologically active" refers to an entity which interacts in some way with a living organism on a molecular level. Entities which are biologically active may activate a receptor, provoke an immune reaction, interact with a membrane or ion channel, or otherwise induce a change in a biological function of an organism or any part of an organism.

The definition above does not encompass stability per se. For instance, a peptide which has some level of stability does not necessarily have some level of biological activity. Applicants also remind the Examiner that MPEP 2111 requires that "during patent Examination, the pending claims must be given their broadest reasonable interpretation consistent with the specification." Accordingly, Applicants contend that the claims in the present application should be given their broadest meaning within the definition of biological activity as defined in the specification. Applicants have amended claims 28, 54, 55 and 80 to clarify the meaning of biological activity as defined in the section of the specification recited above. Applicants submit that the scope of these claims is not narrowed by this amendment, because the proper construction of these claims would have utilized this explicit definition from the specification.

(ii) With regards to the second issue, Applicants contend that while Applicants have argued that the claims are enabled because unpredictability in protein chemistry art does not apply to the instant invention (as put forth for example on pages 16-17 of the response filed July 2, 2002), Applicants have not argued that the full scope of the claims was enabled because the role of SA is a carrier per se. Applicants have merely argued that, in response to the enablement rejection stating that the specification fails to provide what biological activity the peptide must have, the SA serves the role of a "carrier", such that any peptide with any biological activity may be used in the present invention. Again, the Office Action appears to confuse the term carrier with stability.

(iii) With regards to the third issue, Applicants contend that although a chimeric SA having 1000-fold more activity for EC binding than the inserted peptide on its own is indeed an example of increased biological activity, the term "increased biological activity" as recited in the claims should not be limited to mean 1000-fold more activity. Applicants contend that the Examiner is reading limitations into the claim which are not recited in the claims. If Applicants

meant to limit the invention to only those chimeric SA molecules having at least 1000-fold greater activity, then Applicants would amend the independent claims to include such limitations. Further, the Office Action holds the 1000-fold increase in biological activity over the uninserted peptide to be the exception rather than the rule, as not every peptide is expected to show such an increase in biological activity. Again, the claims do not state that the resulting chimeric polypeptides *must* have 1000-fold more activity, just that the chimeric polypeptides show increased biological activity. Thus, whether the Office believes the 1000-fold increase in biological activity to be the exception rather than the rule is irrelevant, since the claims do not require such a 1000-fold-increase.

(iv) Similarly, with respect to the fourth issue, Applicants contend that claim 1 does not recite that the resulting chimeric SA must have 1000-fold more activity, and therefore the allegation that the specification does not teach how to achieve this characteristic is irrelevant. Accordingly, Applicants request that this ground of rejection be removed in light of these comments and those presented in the previous responses, since the Office Action incorrectly interpreted the claims.

(v) With regards to the fifth issue, which asserts that if Applicants maintain that the claimed invention is a product with 1000-fold more activity than the inserted peptide, then the written description rejection withdrawn in the Office Action mailed on 9-24-2002 will be reinstated, Applicants again reiterate that the claim is not directed specifically to SA chimeras having 1000-fold greater activity than the inserted peptide, but rather to SA chimeras that have an increased biological activity. Accordingly, Applicants are not asserting that the claimed invention is a product with 1000-fold greater biological activity than the inserted peptide, and therefore the written description rejection withdrawn in the Office Action mailed on 9-24-2002 need not be reinstated. Furthermore, even if the alleged written description rejection were reinstated, Applicants direct the Examiner's attention to the arguments set forth in the Communication filed on July 5, 2005, pages 18-23, detailing why the written description rejection is improper. If the written description rejections are reinstated, Applicants request that the arguments raised by Applicants in response to the written description rejection in the aforementioned Communication be fully considered and addressed in any subsequent Office Action.

Claim rejections under 35 U.S.C. 102

Claims 28, 54, 55-77, and 93-104 are rejected under 35 U.S.C. 102(b), as being anticipated by WO 95/30759 ("the '759 publication" thereafter) as evidenced by Zetter and by Fixe.

Applicants note that the Office Action has not fully considered the Applicants arguments traversing this ground of rejection set forth in the previous Communication filed August 21, 2003, since the Office Action contends that the issue of half-life and increased biological activity, as described in the section above, had not been settled. Applicants contend that the issue has been clarified both by the comments in the preceding section and by the amendment to the claims and reiterate the Applicant's position that "increased biological activity" is not the same as "enhanced stability."

Applicants again traverse the Office Action's rejection. The previous Office Action asserted that the '759 publication teaches that a chimeric polypeptide with a useful heterologous peptide inserted anywhere within serum albumin (SA) can be derived from various therapeutically useful proteins, including an angiogenesis-inhibiting protein or a protein that binds to receptor tyrosine kinase (RTK). The '759 publication also allegedly teaches chimeras with increased *in vivo* stability. The Office Action acknowledges that the '759 publication does not specify the functional property of the various useful proteins, a laundry list of functional properties are listed in pages 3 and 4, also in claim 3 of the '759 publication. Thus the Office Action concludes that the functional properties are inherent properties of the useful proteins. To support this, the Office Action also refers to Fixe to show that it was well known in the art that M-CSF is a RTK (note: should be "ligand for RTK"), and that an active portion of M-CSF inserted into the SA protein would bind to a cell surface receptor or RTK. Similarly, the Office Action refers to Zetter which shows that angiostatin and endostatin are well known in the art as angiogenesis-inhibiting proteins useful for cancer treatment.

A. Failure of Cited References to Teach All Limitations of Claimed Invention

Applicants submit that the claimed invention is a chimeric SA polypeptide that "exhibits

increased biological activity relative to the heterologous peptide sequence itself." (emphasis added). Contrary to assertions in the Office Action, the claimed invention is not limited to those polypeptides exhibiting a 1000-fold increase in biological activity but more generally to those exhibiting increased biological activity when compared to the uninserted heterologous peptide itself. As asserted before, "increased biological activity" is not the same as "enhanced stability." Thus the '759 publication fails to teach each and every aspect of the claimed invention and reference to Zetter or Fixe does not correct this defect. Therefore, the cited references fail to anticipate the claimed invention.

As argued before, the specification indicates, on page 44, second paragraph, that the EC binding peptides inserted into mouse serum albumin actually exhibit 1000-fold more activity than the uninserted synthetic peptides themselves. The chimeric polypeptide is effective in inhibiting EC cell proliferation at nanomolar concentrations, while the uninserted peptide is effective only in the millimolar range.

In contrast, the '759 publication is completely silent about the chimeric proteins actually having any biological activity of the inserted peptide, much less about chimeric proteins actually having increased biological activity relative to the inserted peptide. It is merely *hoped* that a chimeric polypeptide might possess, at most, enhanced stability, which the '759 publication never shows. Furthermore, the '759 publication also fails to describe even an intention to compare biological activity of the chimeric SA to that of the uninserted peptide to determine if the chimeric SA exhibits an increased biological activity over the uninserted peptide, thus failing to put the claimed invention in possession of the public, as is legally required for anticipation (see below). Reference to Zetter or Fixe does not correct this defect.

The '759 publication contains no working examples of a chimeric SA showing a biological activity of the inserted peptide. The '759 publication provides two experimental examples of the purification from yeast of albumin proteins containing insertion of heterologous sequences. No functional characterization of any kind is performed *in vitro* or *in vivo* on the two chimeric proteins to test if the SA proteins retain or exceed the biological activity of the uninserted peptide. Thus, these two examples amount to no more than a routine exercise in recombinant protein production, where no indication of any biological activity is provided, much less of chimeric proteins having increased biological activity over the uninserted peptide. The

last example of the '759 publication describes a hypothetical chimeric albumin protein containing a cleavage site for the factor Xa protease inserted at amino acid 58. No data or evidence is provided in this hypothetical example or anywhere else in the '759 reference that any insertions in albumin result in chimeric proteins that retain any of the biological activity of the inserted peptide, much less having increased biological activity. Accordingly, the '759 publication teaches no working examples of chimeric SA proteins having any of the biological activity of the inserted peptides. The '759 publication merely presents, at most, an exercise in standard cloning techniques. Because the '759 publication does not teach chimeric SA proteins having an increased biological activity relative to the inserted peptide, and reference to Zetter or Fixe does not correct this defect, the cited references fail to teach every limitation of the claimed invention, and therefore they do anticipate the claimed invention.

And even assuming, for the sake of argument, that what the '759 publication taught chimeric SA having increased stability relative to the inserted peptides, enhanced stability is still quite different from increased biological activity, as claimed in the instant application. As a skilled artisan would appreciate, two otherwise identical polypeptides may have the same stability (for example, life-span in serum), but can have dramatically different overall biological activities, no less potencies, due to factors such as conformation in a specific solution. Another distinction between "increased biological activity" and "enhanced stability" is that the former usually requires the polypeptide to have some kind of activity of its own (such as being able to act on a target molecule), while the later simply requires the polypeptide to be stable (see above), even though it may not have any activity at all.

Applicants further contend that they have never conceded that the '759 publication actually shows increased stability (see above and more below), nor equated "increased half-life (stability)" to "increased biological activity." In arguments filed with previous responses, Applicants' position is that the examples of the instant specification demonstrate that cysteine loops of SA provide an effective "expression cassette" which allows the expression of such "active heterologous peptides" with increased stability, and retained/increased potency (see above). Therefore, "increased potency" is recited in addition to "increased stability." Applicants have clearly conveyed the idea that increased biological activity may not be fully accounted for by increased stability alone (also see below).

B. Failure to Inherently Anticipate the Claimed Invention

Applicants further submit that the '759 publication, alone or in further view of Zetter or Fixe, fails to inherently anticipate the claimed invention. Pursuant to MPEP 2112, "Examiner must provide rationale or evidence tending to show inherency." The same section of MPEP further states that "[t]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)," (emphasis in original), and that "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.' *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)."

The '759 publication at best hoped for a serum albumin chimera with enhanced half-life with regard to the inserted heterologous polypeptide, while containing no actual examples of SA chimera displaying such properties. The '759 publication at best enables a skilled artisan to make and use a chimera of increased half-life, but does not teach or suggest that an inserted heterologous polypeptide may exhibit an unexpectedly *increased biological activity*. In other words, the potentially "inherent characteristic" – increased biological activity – does not *necessarily* flow from the disclosure of the '759 publication, or from that of the '759 publication as evidenced by Zetter and Fixe, especially since increased-half-life is not the same as increased biological activity. Thus, the cited references fail to inherently anticipate the claimed invention.

Therefore, the '759 publication, alone or in further view of Zetter or Fixe, does not teach or suggest each and every aspect of the claimed invention, and does not inherently anticipate the claimed invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim rejections under 35 U.S.C. 103(a)

Claims 29-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over the '759 publication as applied to claims 28, 54, and 55 above, further in view of the specification at pages 16-22.

The Office Action asserts on page 4, lines 9-10 that "Applicants argues WO/9530759 is not art but this argument is not persuasive for reasons given in 102(b) rejection above." In this and previous communications, Applicants have traversed the 102 rejections, in part, by showing that the cited references fail to teach all the limitations and to inherently anticipate the claimed invention. Accordingly, in light of those arguments and the ones that follow, Applicants request reconsideration and withdrawal of this ground of rejection.

Pursuant to MPEP 706.02(j), three basic criteria have to be met before a *prima facie* case of obviousness can be made: 1) the prior art references must teach or suggest all the claim limitations; 2) some motivation or suggestion, either found in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine or modify the references must be present; and 3) a reasonable expectation of success is required.

The alleged case of prima facie obviousness in the Office Action fails, in part, because the cited references fail to teach or suggest all the claim limitations of the invention.

Claims 29-33 are directed to delivery vectors and transfected cells comprising the nucleotide of claim 28, thus these claims are non-obvious if claim 28 is non-obvious. Applicants submit that the claimed invention is non-obvious over the '759 publication, since the '759 publication never teaches or suggests that an inserted heterologous polypeptide may have increased biological activity over the inserted peptide, as taught in the instant specification. The '759 application describes the purification of two chimeric SA proteins and one prophetic example, but does not actually perform, teach or suggest testing to determine if the inserted peptides have increased biological activity over the uninserted peptide. Applicants further direct the Examiner's attention to the arguments above in response to the 102 rejection detailing why the '759 does not teach or suggest all the limitations of the claimed invention.

Not only does the '759 publication fail to teach or suggest all the limitations of the claimed invention, Applicants have shown unexpected results sufficient to rebut an obviousness rejection. The increase of biological activity of the EC binding peptides disclosed in the specification is a dramatic increase in activity and an unexpected result that could not have been predicted based on the collective teachings of any cited prior art references.

Thus, Applicants request reconsideration and withdrawal of this ground of rejection.

Claims 80-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over the '759 publication as applied to claims 28, 54, and 55 above, further in view of Cardarelli.

Specifically, the Office Action asserts that the claimed invention recites "at least two inserted heterologous polypeptides," which is allegedly an obvious variation of the cited primary reference disclosure "at least one active" heterologous polypeptide, since Applicants do not show any unexpected results. Further, Cardarelli teaches "RGD is well known in the art."

As argued above, claim 80 and its dependent claims also contain the "increased biological activity" feature, which is not taught or suggested by any of the cited references or combinations thereof, assuming for the sake of argument that such combination would be made by a skilled artisan. Furthermore, as stated above, Applicants have presented unexpected results which sufficient to rebut an obviousness rejection. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 85-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over the '759 publication as applied to claims 28 above, further in view of Carter *et al.*

Specifically, the '759 publication allegedly teaches that any therapeutically desirable peptide can be inserted into any location within SA. However, the Office Action acknowledges that the '759 publication does not specifically teach insertion of the heterologous peptide into a portion of a Cys loop of a SA protein. The Office Action also alleges that the '759 publication teaches in Figure 1 that SA has extensive Cys loops, and that Carter teaches the crystal structure of SA with "several surface exposed cysteine loops (see page 167-173)." The Office Action contends that, since the specification does not teach any unexpected results with the specific cysteine loops, which are already known in the art, it is an obvious variation of the teaching of the primary references.

Applicants traverse the rejection. Claim 28, as well as dependent claims 85-88, contain the "increased biological activity" feature, which is not taught or suggested by any of the cited references or combinations thereof, assuming for the sake of argument, that such combination would be made by a skilled artisan. Furthermore, as stated above, Applicants have presented unexpected results sufficient to rebut an obviousness-type rejection. Reconsideration and withdrawal of the rejection are respectfully requested.

Applicants contend that even if the cited art were to teach an SA chimera having an increased biological activity, the cited references still would not teach or suggest all the claim limitations of claims 85-88, as these claims recite insertion of the peptides at cysteine loops and this limitation is not taught or suggested by the cited references as explained below. Furthermore, there would be no reasonable expectation of success at arriving at the claimed invention, as required by MPEP 706.02(j), and thus a case of prima facie obviousness would not be made.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicant's disclosure. Using Applicants' disclosure as a template for picking and choosing from amongst the prior art to reconstruct the claimed invention is not permitted. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Thus, to render the claimed invention obvious, all three criteria must be met.

Regarding the insertion site, the '759 publication suggests that the heterologous peptide may be inserted into sites that "are preferably localized in the regions of the albumin presumed to form exposed regions at the surface of the molecule, these regions preferably being loops" (page 7, lines 3-5). However, contrary to the Office Action's assertion, the '759 publication never teaches or suggests that any of these sites could be cysteine loops as claimed in the instant application. In fact, the '759 publication does not refer to any cysteine loops at all. Instead, the '759 publication suggested a few preferred insertion sites as "residues 57-62 (region 5) which corresponds to a loop connecting helices h3 and h4; residues 103-120 which corresponds to the zone between subdomains (region 8, an alpha helix structure, not a loop at all); residues 178-200 which corresponds to a helix (region 13, another alpha helix, not a loop at all); and residues 419-430 which corresponds to a region defined by helices h2 and h3 of domain III (not a Cys loop). Aside from region 5, which partially overlaps with one of the claimed Cys loops, none of these preferred sites actually corresponds to any of the claimed Cys loops. Even though the '759 publication suggests that the insertion sites are preferably exposed surface loops, there are many different surface loops in the SA structure. This genus of "exposed surface loop structure" does not anticipate the claimed Cys loops, one particular species of the exposed surface loops. Neither would this genus of loops specifically suggest that one of ordinary skill look for Cys loops on

the surface of SA. The advantage of the Cys loop, first recognized by the present inventors, partly resides in the fact that these loops are structurally constrained by the disulfide bonds forming these loops, and thus a peptide inserted within the Cys loop is much less likely to disrupt the overall structure of the chimeric protein, while a peptide inserted in a non-constrained loop or helix structure is more likely to disrupt the overall structure and/or stability of the chimera. This concept was neither taught nor suggested by the '759 publication. In fact, Figure 1 of the '759 publication actually shows many potential loop-like structures between the helices. These loops are not necessarily linked by disulfide bonds (see, for example, the loops between h2 and h3, between h6 and region 8, between region 8 and h7, etc.).

On the other hand, Carter is a review article relating to the structure of SA. In the passage cited by the Office Action (pages 167-173, especially Figure 10 and Table II), Applicants were unable to find any specific reference to "surface exposed cysteine loops," as recited in the Office Action. The only passages relating to the "Cys loop" seem to be descriptions for "disulfide bridges" (see page 169, last line; several occurrences on page 170; and page 171, section "b"). But none of these passages seems to indicate that any Cys loops are actually "surface exposed," let alone suitable to serve as potential insertion sites for heterologous proteins. Thus, Carter also does not suggest Cys-constrained surface-exposed loops claimed in the instant application. Applicants respectfully request that the Examiner point out / recite specific sentences or passages from Carter which clearly indicate that serum albumin has several "surface exposed cysteine loops" as recited in the Office Action.

In view of the above remarks, even if a skilled artisan were motivated to combine the '759 publication with Carter, the artisan would not specifically look for Cys loops as claimed in the instant application. Thus the combined teachings of the '759 publication and Carter still fail to guide a skilled artisan to arrive at the claimed invention, and do not teach or suggest all the limitations of the claimed invention. Applicants further submit that a skilled artisan would also lack a reasonable expectation of success in arriving at the claimed invention (chimeric SA polypeptide containing a heterologous polypeptide inserted into the Cys loop(s) and with an increased biological activity).

As argued above, the cited art disclosed the fusion of heterologous peptides to either the N- or the C-terminus of SA, but, except for the '759 publication, did not disclose insertion of

heterologous peptides into the SA. Moreover, none of these references teaches or suggests that an inserted heterologous peptide may have *increased* biological activity compared to the uninserted counterpart. Thus, a skilled artisan would have no reasonable expectation that an inserted heterologous peptide would actually show *increased* biological activity. Indeed, the *increased* biological activity is an unexpected result that is not obvious in view of the prior art teaching.

Accordingly, despite the generic teachings of the '759 publication, a skilled artisan would have had no reasonable expectation of success in arriving at the claimed invention. In other words, until Applicants demonstrated that the chimeric albumins could indeed exhibit dramatic (in the present case, about 1000-fold) increase in biological activity, *a priori*, one of ordinary skill in the art would not have had a reasonable expectation for success based on the teachings of the '759 publication and the knowledge available in the prior art. In addition, the skilled artisan would also lack motivation to pick the Cys loops recited in the claims, and insert heterologous, biologically active peptides into these constrained Cys loop sites, since the natural conformation of the inserted peptide might be too distorted to maintain activity.

In view of the foregoing, Applicants submit that all three requirements for making a *prima facie* case of obviousness are not met. Accordingly, reconsideration and withdrawal of rejection under 35 U.S.C. 103(a) are respectfully requested.

Double Patenting Rejections

The Office Action states that claims 28-33, 54-84, 93-104 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 28-33 and 49-91 of the co-pending U.S. Application 09/619,285.

Applicants submit that, pursuant to MPEP 804, "[i]f the 'provisional' double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent [without filing a terminal disclaimer], thereby converting the 'provisional' double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent."

If conflicting claims are first allowed in the co-pending U.S. Application 09/619,285 and appear in an issued U.S. patent, Applicants note that, pursuant to 37 CFR 1.130(b), a timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome the double patenting rejection. Applicants will submit a terminal disclaimer, if necessary, upon indication of allowable subject matter.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 212-497-3613. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945** under Order No. GPCI-P03-109.

Dated: February 4, 2004

Respectfully submitted,

By _____

Ignacio Perez de la Cruz
Registration No.: P55,535
ROPES & GRAY LLP
45 Rockefeller Plaza
New York, NY 10111
(212) 497-3613
(212) 497-3650 (Fax)
Attorneys/Agents For Applicant